
Case report

Myocardial infarction during intravenous immunoglobulin infusion in a 65-year-old man with common variable immunodeficiency and subsequent successful repeated administration

Shoban Davé, MD, and John Hagan, MD

Background: Intravenous immunoglobulin (IVIG) may cause thromboembolic events. Although such events are usually associated with large IVIG doses administered to treat neurologic diseases, thromboembolic events may also occur with standard immunodeficiency doses.

Objective: We describe a 65-year-old man with common variable immunodeficiency (CVID) who experienced angina and myocardial infarction with IVIG infusion.

Methods: The patient's electronic medical record was reviewed.

Results: The patient developed substernal chest pain during a scheduled 40-g (400-mg/kg) infusion. The infusion was discontinued, and a cardiac evaluation was initiated. The patient was found to have elevated troponin T and creatine kinase MB levels, signifying cardiac injury. Heart catheterization revealed severe vessel disease, and surgical revascularization was subsequently performed. Three weeks after revascularization, an IVIG dose of 200 mg/kg was cautiously readministered. This dose was increased in 2 weeks to 300 mg/kg, which was tolerated every 3 to 4 weeks without any adverse thrombotic events in the subsequent 12 months.

Conclusions: This case demonstrates not only angina and myocardial infarction associated with IVIG infusion in a patient with CVID but also the successful reinitiation of IVIG infusion after surgical revascularization. This case also underscores the importance of caution with IVIG infusion in patients with CVID and known coronary artery disease.

Ann Allergy Asthma Immunol. 2007;99:567–570.

INTRODUCTION

Intravenous immunoglobulin (IVIG) is used to treat a variety of conditions, including common variable immunodeficiency (CVID), a primary humoral immunodeficiency characterized by recurrent bacterial infections, lymphoproliferation, granulomatous disease, autoimmunity, and hypogammaglobulinemia.^{1,2} Treatment doses of IVIG in CVID are typically 0.4 g/kg per month and mitigate the infection rate and pulmonary complications.³ The dose used in CVID contrasts the larger immunomodulatory doses of IVIG used in the treatment of autoimmune and neurologic conditions.³ Larger doses predispose to adverse thromboembolic events, including myocardial infarction (MI)⁴; however, the association of thromboembolic events with replacement doses of IVIG is less frequently reported. We describe a patient with CVID who experienced angina

and an MI during an infusion with replacement IVIG. He subsequently underwent revascularization and successfully tolerated readministration of IVIG.

CASE REPORT

A 65-year-old man with a 9-year history of CVID was treated for 6 years with monthly IVIG (Polygam S/D 10%; Baxter Healthcare Corp, Deerfield, Illinois) without complications. He also had a history of coronary artery disease (CAD) that had previously required coronary artery bypass grafts and percutaneous intervention before his diagnosis of CVID. Initial immunoglobulin levels were as follows: IgA, less than 6.7 mg/dL (reference range, 50–400 mg/dL); IgM, 15.6 mg/dL (reference range, 50–300 mg/dL); IgG, 98 mg/dL (reference range, 600–1,500 mg/dL); and IgE, less than 2.0 kU/L (mean, 13.2 kU/L). Additional immunologic studies revealed normal differential and complete blood cell counts and a normal total hemolytic complement assay level. Complications of his CVID included non-Hodgkin lymphoma, squamous cell carcinoma of the tongue, granulomatous hepatitis, and rheumatoid arthritis. Cardiac risk factors included previous CAD, hy-

Division of Allergic Diseases, Department of Medicine, Mayo Clinic, Rochester, Minnesota.

Authors have nothing to disclose.

Received for publication March 22, 2007.

Received in revised form June 29, 2007.

Accepted for publication July 17, 2007.

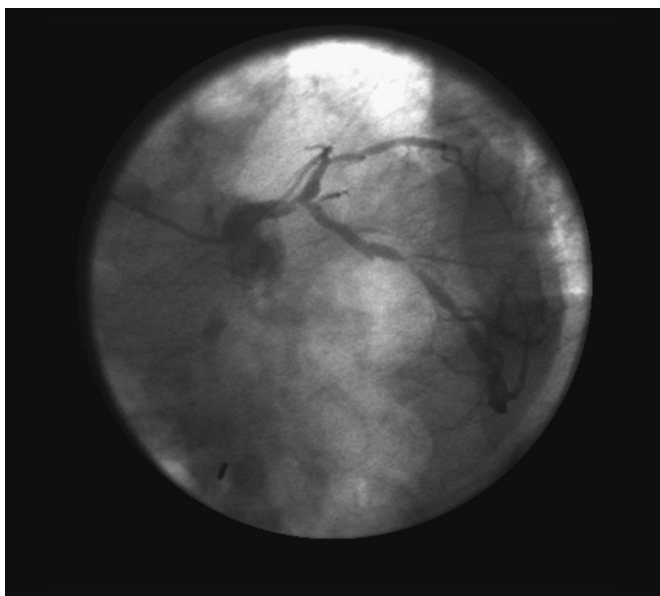


Figure 1. Left heart catheterization image revealing high-grade left main and midcircumflex coronary artery disease.

pertension, hyperlipidemia, and diet-controlled type 2 diabetes mellitus. His current medications were aspirin (325 mg orally daily), atorvastatin (10 mg orally daily), atenolol (25 mg orally twice daily), isosorbide (10 mg orally once daily at bedtime), and amlodipine (10 mg orally daily). He also had a history of aortic and renal artery stenosis and hyperparathyroidism with previous parathyroidectomy.

Because Polygam was removed from the market, the patient received his first infusion of 40 g (400 mg/kg) of Gammagard S/D 10% (Baxter Healthcare Corp). This product contained 4% glucose and IgA ($\leq 4.4 \mu\text{g/mL}$). He received the infusion at 1 mL/min for the first 30 minutes, followed by 2 mL/min for 30 minutes and then 3 mL/min for 30 minutes. Toward the end of the infusion cycle, he experienced the sudden onset of chest discomfort with radiation to both shoulders and arms. He rated this chest pain as 8 of 10, and the IVIG infusion was immediately stopped according to the infusion center protocol. He experienced no accompanying nausea, vomiting, shortness of breath, or diaphoresis. The angina persisted for approximately 1 hour despite ingestion of 2 sublingual nitroglycerin tablets, and he was transferred to the emergency department (ED). Although he had never experienced anginal episodes with previous IVIG infusions, he had chronic stable angina with exercise that required preexercise isosorbide therapy. Most recently, he experienced angina while walking on a treadmill approximately 1 week before this infusion event.

In the ED he was afebrile, with a heart rate of 57/min; blood pressure, 112/70 mm Hg; respiratory rate, 20/min; and pulse oximetry, 97% on a 2-L nasal canula. On exam-

ination, this patient was in no apparent distress. Heart examination revealed a regular rate and rhythm without murmurs, rubs, or gallops. Lungs were clear to auscultation bilaterally.

Electrocardiography showed a normal sinus rhythm without evidence of acute ischemia or injury. A chest radiograph revealed postoperative changes consistent with previous cardiac surgery but was otherwise normal. Initial cardiac biomarkers of creatine kinase, creatine kinase MB, and troponin T were all normal. The patient was treated with intravenous nitroglycerin and morphine. He soon experienced relief of his chest discomfort.

The allergy service of Mayo Clinic was not consulted during his ED evaluation or by the admitting team, and IVIG infusion was reinitiated in the hospital at the request of the patient and his wife, who felt that "IVIG is expensive and we want the rest of the bag to be given." With this verbal consent, the IVIG infusion (22 g) was reinitiated at a rate of 3 mL/min, during which the patient had recurrence of chest discomfort. The IVIG infusion was discontinued, and the angina lasted approximately 40 minutes. Subsequent inpatient evaluation revealed an elevated creatine kinase MB fraction of 15.9 ng/mL (reference range, $\leq 6.2 \text{ ng/mL}$) and troponin T level of 0.37 ng/mL (reference range, $\leq 0.03 \text{ ng/mL}$), signifying cardiac injury. The patient was treated with a standard acute coronary syndrome protocol of aspirin, atenolol, atorvastatin, intravenous heparin, isosorbide dinitrate, and morphine. Left heart catheterization revealed severe 3-vessel coronary artery and coronary graft disease (Fig 1). The patient underwent repeat surgical revascularization 2 weeks later.

Given the severity of his underlying CVID, this patient required readministration of IVIG. Three weeks after surgery, he received 200 mg/kg of IVIG (Gammagard S/D 10%), which was increased in 2 weeks to 300 mg/kg. Infusions of IVIG were initiated at 1 mL/min for the first 30 minutes, followed by 2 mL/min for 30 minutes and then 3 mL/min for 30 minutes and 4 mL/min for 30 minutes. The goal was to achieve an IgG trough level of 600 to 800 mg/dL to reduce the risk of infection while anticipating medical procedures for squamous cell carcinoma. Subcutaneous therapy was rejected by the patient. Although the final rate (2.4 mL/kg per hour) slightly exceeded the 1 to 2 mL/kg per hour recommended by Brown and Ballas⁵ for patients with vascular risk factors, this protocol using a 300-mg/kg dose with a final rate of 4 mL/min was tolerated every 3 to 4 weeks for 12 months without subsequent adverse thrombotic events since revascularization.

DISCUSSION

IVIG is manufactured from pooled human plasma and primarily consists of polyvalent IgG. Plasma pools range from 4,000 to more than 50,000 L⁶ and are obtained from 3,000 to more than 60,000 human donors.⁷ Alcohol fractionation, antiaggregation, and stabilization of this pooled plasma results in

a solution containing 95% to 99% IgG⁷ and varying amounts of albumin, IgA, IgE, and IgM.⁶

IVIG is generally well tolerated; however, its use is known to carry risk. A survey conducted by the Immune Deficiency Foundation of more than 1,000 patients found that 44% of those treated with IVIG had previously experienced a side effect, most commonly reported by patients to be headache, fever, nausea, vomiting, and chills.⁸ Adverse event incidences, including rate-related and serious adverse events, on a per-infusion basis given for a variety of indications may vary from 2% to 25%.⁹ Most reactions are mild and transient and are attributed to accumulation of IgG aggregates and IgG dimers and to complement activation.¹⁰ Common reactions include fever, headache, myalgia, chills, nausea, vomiting, lightheadedness, back or leg pain, rash, flushing, pruritus, hypotension, hypertension, and fluid overload.⁷ More serious adverse effects of IVIG infusion include acute renal failure, anaphylaxis, aseptic meningitis, and thromboembolic events.

To our knowledge, this case is the first to describe an MI caused by replacement doses of IVIG in a patient with CVID. Brown and Ballas⁵ reported 3 patients with immunodeficiency treated with replacement doses of IVIG who experienced cerebrovascular accidents or transient ischemic attacks. Thromboembolic events associated with IVIG infusion may manifest in arterial and venous systems. Reported manifestations of thromboembolism with IVIG infusion include cerebrovascular accidents, MI, pulmonary embolus, and deep vein thrombosis.¹⁰ Thromboembolic events occur more frequently when immunomodulatory dosed IVIG is used compared with the replacement doses (200–600 mg/kg per month) used in immunodeficiencies.⁵ In patients with risk factors, Brown and Ballas⁵ recommend that iso-osmolar preparations of IVIG be given at rates not to exceed 1 to 2 mL/kg per hour. This patient's infusion rate was 1.8 mL/kg per hour (3 mL/min) at the time of angina. Concerns about the potential adverse effect of thromboembolic disease have been added to recent parameters concerning patients with primary immunodeficiency.³

It has been proposed that patients with advanced age, CAD, diabetes mellitus, hyperlipidemia, hypertriglyceridemia, hypertension, hypercoagulable states, cryoglobulinemia, paraproteinemia, polycythemia, and decreased cardiac output and those receiving high-dose IVIG or IVIG with a rapid infusion rate are at particular risk for thromboembolism.^{9–11} Several hypothesized mechanisms of thromboembolism are unique to IVIG infusion. Mechanisms most implicated as causes are IVIG-induced increases in blood viscosity^{12,13}; adenosine triphosphate release, which may aid in platelet aggregation¹⁴; red blood cell aggregation in the presence of elevated albumin or fibrinogen levels¹⁵; complement activation^{16,17}; arterial vasospasm with plaque disruption¹⁸; release of vasoconstrictive cytokines, including IL-6 and thromboxane B₂¹⁹; and IVIG product contamination with factor XI, a procoagulant.²⁰

In conclusion, this case demonstrates angina and MI associated with IVIG infusion in treatment doses far less than those used for idiopathic thrombocytopenia and neurologic disease. Furthermore, this case demonstrates the successful reintroduction of IVIG in a patient with CVID after cardiac revascularization. This case also underscores the importance of caution with IVIG infusion in patients with CVID and known CAD and suggests the need for thromboembolic risk factor evaluation and possible pharmacologic prophylaxis (eg, aspirin). Allergists should continue to encourage regular health care maintenance, including preventive cardiac care, in patients with CVID treated with IVIG.

REFERENCES

1. Goldacker S, Warnatz K. Tackling the heterogeneity of CVID. *Curr Opin Allergy Clin Immunol*. 2005;5:504–509.
2. Conley ME, Notarangelo LD, Etzioni A; PAGID (Pan-American Group for Immunodeficiency) and ESID (European Society for Immunodeficiencies). Diagnostic criteria for primary immunodeficiencies. *Clin Immunol*. 1999;93:190–197.
3. Orange JS, Hossny EM, Weiler CR, et al. Use of intravenous immunoglobulin in human disease: a review of evidence by members of the Primary Immunodeficiency Committee of the American Academy of Allergy, Asthma and Immunology. *J Allergy Clin Immunol*. 2006;117:S525–S553.
4. Hefer D, Jaloudi M. Thromboembolic events as an emerging adverse effect during high-dose intravenous immunoglobulin therapy in elderly patients: a case report and discussion of the relevant literature. *Ann Hematol*. 2004;83:661–665.
5. Brown HC, Ballas ZK. Acute thromboembolic events associated with intravenous immunoglobulin infusion in antibody-deficient patients. *J Allergy Clin Immunol*. 2003;112:797–799.
6. Martin TD. IGIV: contents, properties, and methods of industrial production: evolving closer to a more physiologic product. *Int Immunopharmacol*. 2006;6:517–522.
7. Kumar A, Teuber SS, Gershwin ME. Intravenous immunoglobulin: striving for appropriate use. *Int Arch Allergy Immunol*. 2006;140:185–198.
8. Immune Deficiency Foundation. *Treatment Experiences and Preferences of Patients With Primary Immune Deficiency Disorders: First National Survey*. Towson, MD: Immune Deficiency Foundation; 2003.
9. Pierce LR, Jain N. Risks associated with the use of intravenous immunoglobulin. *Transfus Med Rev*. 2003;17:241–251.
10. Orbach H, Katz U, Sherer Y, Shoenfeld Y. Intravenous immunoglobulin: adverse effects and safe administration. *Clin Rev Allergy Immunol*. 2005;29:173–184.
11. Looney RJ, Huggins J. Use of intravenous immunoglobulin G (IVIG). *Best Pract Res Clin Haematol*. 2006;19:3–25.
12. Dalakas MC. High-dose intravenous immunoglobulin and serum viscosity: risk of precipitating thromboembolic events. *Neurology*. 1994;44:223–226.
13. Reinhart WH, Berchtold PE. Effect of high-dose intravenous immunoglobulin therapy on blood rheology. *Lancet*. 1992;339:662–664.
14. Woodruff RK, Grigg AP, Firkin FC, Smith IL. Fatal thrombotic events during treatment of autoimmune thrombocytopenia with intravenous immunoglobulin in elderly patients. *Lancet*. 1986;

-
- 2:217–218.
15. Ben-Ami R, Barshtein G, Mardi T, et al. A synergistic effect of albumin and fibrinogen on immunoglobulin-induced red blood cell aggregation. *Am J Physiol Heart Circ Physiol*. 2003;285:H2663–H2669.
16. Wegmuller E. Effect of intravenous immunoglobulin therapy on plasma complement. *Transfus Sci*. 1998;19:307–318.
17. Mollnes TE, Hogasen K, De Carolis C, et al. High-dose intravenous immunoglobulin treatment activates complement in vivo. *Scand J Immunol*. 1998;48:312–317.
18. Voltz R, Rosen FV, Yousry T, Beck J, Hohlfeld R. Reversible encephalopathy with cerebral vasospasm in a Guillain-Barre syndrome patient treated with intravenous immunoglobulin. *Neurology*. 1996;46:250–251.
19. Sherer Y, Levy Y, Langevitz P, Rauova L, Fabrizzi F, Shoenfeld Y. Adverse effects of intravenous immunoglobulin therapy in 56 patients with autoimmune diseases. *Pharmacology*. 2001;62:133–137.
20. Wolberg AS, Kon RH, Monroe DM, Hoffman M. Coagulation factor XI is a contaminant in intravenous immunoglobulin preparations. *Am J Hematol*. 2000;65:30–34.
- Requests for reprints should be addressed to:*
Shoban Davé, MD
Division of Allergic Diseases
Department of Medicine
Mayo Clinic
200 First St SW
Rochester, MN 55905
E-mail: dave.shoban@mayo.edu
-